

PULSATILE RELEASE HISTAMINE H₂ ANTAGONIST DOSAGE FORM

CROSS REFERENCES

This application claims the benefit of U.S. Provisional Application 60/340,419 filed December 14, 2001 and U.S. Patent Application 10/057,759 filed January 25, 2002.

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TECHNICAL FIELD

A major objective of chronotherapy for indications such as asthma, gastric acid secretion and cardiovascular diseases is to deliver the drug in higher concentrations during the time of greatest need and in lesser concentrations when the need is less. Symptoms associated with "GERD" (Gastro Esophageal Reflux Disease) vary in severity throughout a 24-hour period. Accordingly, higher plasma concentrations of a histamine H₂ antagonist, such as nizatidine, are required to provide relief from acid secretion in response to fatty meals, as well as to attenuate the "midnight gerd" seen to occur in patients in response to the circadian rhythm to gastric acid secretion, while lower plasma concentrations are adequate in early morning hours and between meals. This is accomplished by administering a pulsatile release dosage form of the present invention, which provides a controlled release of an histamine H₂ antagonist from properly designed dosage forms. In particular, the present invention relates to a unit dosage form of an assembly of two or more bead populations, each of which is designed to release the therapeutic agent as a rapid or sustained release pulse after a predetermined delay with resulting plasma concentration varying in a circadian rhythm fashion, thereby enhancing patient compliance and therapeutic efficacy, reducing both cost of treatment and side effects.

BACKGROUND OF THE INVENTION

Many therapeutic agents are most effective when made available at a constant rate at or near the absorption site. The absorption of therapeutic agents thus made available generally result in desired plasma concentrations leading to maximum efficacy, minimum toxic side effects. Much effort has been devoted to developing sophisticated drug delivery systems, such as osmotic devices, for oral application. However, there are instances where maintaining a constant blood level of a drug is not desirable. For example, a "position-controlled" drug delivery system

(e.g., treatment of colon disease or use of colon as an absorption site for peptide and protein based products) may prove to be more efficacious. A pulsatile delivery system is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. However, there are only a few such orally applicable pulsatile release systems due to the potential limitation of the size or materials used for dosage forms. Ishino et al. disclose a dry-coated tablet form in Chemical Pharm. Bull. Vol. 40 (11), 3036-041 (1992). U. S. Pat. No. 4,851,229 to Magruder et al., U. S. Pat. No. 5,011,692 to Fujioka et al., U. S. Pat. No. 5,017,381 to Maruyama et al., U. S. Pat. No. 5,229,135 to Philippon et al., and U. S. Pat. No. 5,840,329 to Bai disclose preparation of pulsatile release systems. Some other devices are disclosed in U. S. Pat. No. 4,871,549 to Ueda et al. and U. S. Pat. Nos. 5,260,068; 5,260,069; and 5,508,040 to Chen. U. S. Pat. Nos. 5,229,135 and 5,567,441 both to Chen disclose a pulsatile release system consisting of pellets coated with delayed release or water insoluble polymeric membranes incorporating hydrophobic water insoluble agents or enteric polymers to alter membrane permeability. U. S. Pat. No. 5,837,284 to Mehta et al. discloses a dosage form which provides an immediate release dose of methylphenidate upon oral administration, followed by one or more additional doses spread over several hours.

Studies have shown that gastric acid secretion, especially the midnight gerd, follows a circadian rhythm. In such cases, administration of a different kind of unit dosage form which delivers the drug in higher concentrations during the time of greatest need, for example, around dinner and close to midnight, and in lesser concentrations at other times, is needed. Commonly assigned and co-pending U.S. application Ser. No. 09/778,645, which is incorporated in its entirety, discloses a pulsatile release system comprising a combination of two or three pellet populations, each with a well-defined release profile. In accordance with the present invention, a plasma profile is obtained which varies in a circadian rhythm fashion following administration of the novel dosage form.

SUMMARY OF THE INVENTION

The present invention provides a pulsatile release, multi-particulate dosage form comprising a mixture of two types of beads comprising a histamine H₂ receptor antagonist: IR (Immediate Release) Beads and TPR (Timed Pulsatile Release) Beads. Release profiles which

approximate the daily fluctuations in gastric acid secretion are obtainable by blending IR Beads and TPR Beads at an appropriate ratio estimated from pharmaco-kinetic modeling. The IR Beads typically comprise two coatings applied to non-pareil seeds (# 25-30 mesh). The first coating contains a histamine H₂ antagonist and a binder, such as hydroxypropyl cellulose. The drug layered beads are coated with a seal coating of Opadry Clear to produce IR Beads. TPR Beads can be produced by applying a second functional membrane comprising a mixture of water insoluble polymer and an enteric polymer to IR Beads, both plasticized polymeric systems being applied from aqueous or solvent based systems.

The pulsatile release oral capsule formulation of the present invention comprises a combination of two types of spherical beads containing the active substance. IR (immediate release) Beads allow immediate release of the active while TPR Beads allow a delayed “burst” release (timed pulsatile release) of the active after a lag of 3-4 hours. When administered at bedtime (capsule containing IR Beads + TPR beads), the immediate release of the active is intended to provide relief from acid secretion in response to the meal, while the delayed “burst” is intended to attenuate the “midnight gerd” seen to occur in patients in response to the circadian rhythm to gastric acid secretion.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in further detail with reference to the accompanying Figures wherein:

Fig. 1 shows Circadian Rhythm variations in gastric acid secretion (Reference: the presentation by Gordon L. Amidon at the Formulation Optimization and Clinical Pharmacology, a Capsugel Sponsored Conference at Tokyo, April 23, 1999, p. 16).

Fig. 2 shows the drug release profiles from Nizatidine Pulsatile Capsules, 150 mg (75 mg IR Beads + 75 mg TPR Beads) of Example 1, wherein the TPR Beads have different pulse coating levels.

Fig. 3 shows the drug release profile for Nizatidine Pulsatile Capsules, 150 mg (75 mg IR Beads + 75 mg TPR Beads) of Example 2.

Fig. 4 shows the target or simulated *in vitro* drug release profile used in PK simulation.

Fig. 5 compares the simulated plasma levels of Nizatidine Pulsatile Capsule versus 300 mg IR Dose following oral administration at (a) night time and (b) day time.

Fig. 6 shows the plasma level of Nizatidine following oral administration in a healthy volunteer when dosed after dinner with Pulsatile Capsule, 150 mg (75 mg IR Beads + 75 mg TPR Beads) (a bimodal display) versus 150 mg IR Dose.

DETAILED DESCRIPTION OF THE INVENTION

The active core of the novel dosage form of the present invention may be comprised of an inert particle or an acidic or alkaline buffer crystal, which is coated with a drug-containing film-forming formulation and preferably a water-soluble film forming composition to form a water-soluble/dispersible particle. Alternatively, the active may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer composition containing the drug substance. The amount of drug in the core will depend on the dose that is required, and typically varies from about 5 to 90 weight %. Generally, the polymeric coating on the active core will be from about 1 to 50% based on the weight of the coated particle, depending on the lag time and type of release profile required and/or the polymers and coating solvents chosen. Those skilled in the art will be able to select an appropriate amount of drug for coating onto or incorporating into the core to achieve the desired dosage. In one embodiment, the inactive core may be a sugar sphere or a buffer crystal or an encapsulated buffer crystal such as calcium carbonate, sodium bicarbonate, fumaric acid, tartaric acid, etc. which alters the microenvironment of the drug to facilitate its release.

To produce Timed Pulsatile Release (TPR) Beads, a water soluble/dispersible drug-containing particle is coated with a mixture of a water insoluble polymer and an enteric polymer, wherein the water insoluble polymer and the enteric polymer may be present at a weight ratio of from 4:1 to 1:1, and the total weight of the coatings is 10 to 60 weight % based on the total weight of the coated beads. The drug layered beads may optionally include an inner dissolution rate controlling membrane of ethylcellulose. The composition of the outer layer, as well as the individual weights of the inner and outer layers of the polymeric membrane are optimized for achieving desired circadian rhythm release profiles for a given active, which are predicted based on *in vitro/in vivo* correlations. In accordance with one embodiment of the present invention, a unit dosage form is provided wherein the unit dose comprises a mixture of immediate release beads (IR Beads, which are drug-containing particles without a dissolution rate controlling polymer membrane) and TPR Beads (drug containing particles with a coating of a blend of water insoluble polymer and enteric polymer exhibiting a lag time of 2-4 hours following oral administration), thus providing a two-pulse release profile. A unit dosage form, which does not

comprise a rapid release bead population acting as a bolus dose, is also an embodiment of the present invention.

The present invention also provides a method of making a pulsatile release dosage form comprising a mixture of two bead populations comprising the steps of:

- 5 1. preparing a drug-containing core by coating an inert particle such as a non-pareil seed, an acidic buffer crystal or an alkaline buffer crystal with a drug and a polymeric binder or by granulation and milling or by extrusion/spheronization to form an immediate release (IR) bead;
2. coating the IR bead with a mixture of plasticized water-insoluble and enteric
10 polymers to form a Timed Pulsatile Release (TPR) bead;
3. filling into hard gelatin capsules IR beads and TPR beads at a proper ratio to produce pulsatile capsules providing the desired release profile.

The release profile for TPR beads can be determined according to the following procedure:

15 Dissolution Procedure:

Dissolution Apparatus: USP Apparatus 2 (Paddles at 50 rpm) using a two-stage dissolution medium (first 2 hrs in 700 mL 0.1N HCl at 37°C followed by dissolution at pH = 6.8 obtained by the addition of 200 mL of pH modifier) and Drug Release determination by HPLC).

20 The TSR Beads prepared in accordance with present invention release, when tested by the above procedure, not more than 25%, more preferably not more than 15%, and most preferably not more than 5% in 2 hours, about 15-80%, more preferably about 20-65%, and most preferably about 30-50% in 3 hours, and not less than 60%, more preferably not less than 70%, and most preferably not less than 80% in 4 hrs.

25 Dosage forms in accordance with the present invention typically comprise a combination of IR Beads and TPR Beads at a ratio from 3:1 to 1:3, preferably a ratio from 2:1 to 1:2. In accordance with certain embodiments, the ratio of IR Beads to TPR Beads is approximately 1:1.

30 The histamine H₂ receptor antagonists suitable for incorporation into these circadian rhythm release (CRR) drug delivery systems include acidic, basic, zwitterion, or neutral bioactive molecules or their salts indicated for the treatment of active duodenal ulcer, such as nizatidine, cimetidine, ranitidine, and famotidine.

An aqueous or a pharmaceutically acceptable solvent medium may be used for preparing drug-containing core particles. The type of film forming binder that is used to bind the drug to the inert sugar sphere is not critical but usually water soluble, alcohol soluble or acetone/water soluble binders are used. Binders such as polyvinylpyrrolidone (PVP), polyethylene oxide, 5 hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), polysaccharides such as dextran, corn starch may be used at concentrations of 0.5 to 5 weight %. The drug substance may be present in this coating formulation in the solution form or may be dispersed at a solid content up to 35 weight % depending on the viscosity of the coating formulation.

The drug substance, a binder such as PVP, a dissolution rate controlling polymer (if 10 used), and optionally other pharmaceutically acceptable excipients are blended together in a planetary mixer or a high shear granulator such as Fielder and granulated by adding/spraying a granulating fluid such as water or alcohol. The wet mass can be extruded and spheronized to produce spherical particles (beads) using an extruder/marumerizer. In these embodiments, the drug load could be as high as 90% by weight based on the total weight of the 15 extruded/spheronized core.

The active containing cores (beads, pellets or granular particles) thus obtained may be coated with one or two layers of dissolution rate controlling polymers to obtain desired release profiles with or without a lag time. The inner layer membrane largely controls the rate of drug release following imbibition of water or body fluids into the core while the outer layer membrane 20 provides for the desired lag time (the period of no or little drug release following imbibition of water or body fluids into the core). The inner layer membrane may comprise a water insoluble polymer, or a mixture of water insoluble and water soluble polymers. Representative examples of water insoluble polymers useful in the invention include ethylcellulose, polyvinyl acetate (Kollicoat SR#0D from BASF), neutral copolymers based on ethyl acrylate and 25 methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups such as Eudragit NE, RS and RS30D, RL or RL30D and the like. Representative examples of water soluble polymers are low molecular weight HPMC, HPC, methylcellulose, polyethylene glycol (PEG of molecular weight > 3000) at a thickness ranging from 1 weight % up to 10 weight % depending on the solubility of the active in water and the 30 solvent or latex suspension based coating formulation used. The water insoluble polymer to water soluble polymer may typically vary from 95:5 to 60:40, preferably from 80:20 to 65:35.

The polymers suitable for the outer membrane, which largely controls the lag time of up to 6 hours may comprise an enteric polymer and a water insoluble polymer at a thickness of 10 to 50 weight %. The ratio of water insoluble polymer to enteric polymer may vary from 4:1 to 1:2, preferably the polymers are present at a ratio of about 1:1. The water insoluble polymer typically used is ethylcellulose.

Representative examples of enteric polymers useful in the invention include esters of cellulose and its derivatives (cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate), polyvinyl acetate phthalate, pH-sensitive methacrylic acid-methacrylate copolymers and shellac.

These polymers may be used as a dry powder or an aqueous dispersion. Some commercially available materials that may be used are methacrylic acid copolymers sold under the trademark Eudragit (L100, S100, L30D) manufactured by Rhom Pharma, Cellacefate (cellulose acetate phthalate) from Eastman Chemical Co., Aquateric (cellulose acetate phthalate aqueous dispersion) from FMC Corp. and Aqoat (hydroxypropyl methylcellulose acetate succinate aqueous dispersion) from Shin Etsu K.K.

Both enteric and water insoluble polymers used in forming the membranes are usually plasticized. Representative examples of plasticizers that may be used to plasticize the membranes include triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate diethyl phthalate, castor oil, dibutyl sebacate, acetylated monoglycerides and the like or mixtures thereof. The plasticizer may comprise about 3 to 30 wt.% and more typically about 10 to 25 wt.% based on the polymer. The type of plasticizer and its content depends on the polymer or polymers, nature of the coating system (e.g., aqueous or solvent based, solution or dispersion based and the total solids).

In general, it is desirable to prime the surface of the particle before applying the pulsatile release membrane coatings or to separate the different membrane layers by applying a thin hydroxypropyl methylcellulose (HPMC) (Opadry Clear) film. While HPMC is typically used, other primers such as hydroxypropylcellulose (HPC) can also be used.

The membrane coatings can be applied to the core using any of the coating techniques commonly used in the pharmaceutical industry, but fluid bed coating is particularly useful.

The present invention is applied to multi-dose forms, i.e., drug products in the form of multi-particulate dosage forms (pellets, beads, granules or mini-tablets) or in other forms suitable for oral administration.

The following Examples illustrate the dosage formulations of the invention.

5 **Examples**

Pulsatile Release capsules of nizatidine, a novel histamine H₂ receptor antagonist, comprise a mixture of two sets of beads: The first set is referred to as immediate release (IR) Beads and are designed to provide a loading dose by releasing all of the nizatidine within the first hour, preferably within the first 30 minutes. The second set is referred to as the Timed
10 Pulsatile Release (TPR) Beads and are designed to release nizatidine in a 'burst' over a period of 2 hours after about 2-4 hour lag time. The TPR Beads are produced by applying an outer layer of pulse coating (comprising a blend of an enteric polymer such as HPMCP and a water insoluble polymer such as ethylcellulose) on IR Beads. The two sets of beads when filled into capsule shells at an appropriate ratio will produce the target circadian rhythm release profile
15 required for maintaining drug plasma concentrations at potentially beneficial level when taken orally twice a day, after breakfast and dinner.

Example 1

Nizatidine (5787.7 g) was slowly added to an aqueous solution of hydroxypropylcellulose such as Klucel LF (643.1 g) and mixed well. # 25-30 mesh sugar spheres (3700 g) were coated
20 with the drug suspension in a Glatt fluid bed coater. The drug containing particles were dried, and a seal coat of Opadry Clear (2% w/w) was first applied. These drug containing IR Beads were provided with an outer membrane by spraying a solution of 1:1 blend of ethylcellulose and HPMCP plasticized with diethyl phthalate in 98/2 acetone/water in a fluid bed coater for a weight gain of approximately 39-40%. The coated particles are cured at 60°C until the polymers
25 were coalesced to produce TPR Beads. Pulsatile Release Nizatidine Capsules, 150 mg, were manufactured by filling 75 mg IR Beads and 75 mg TPR Beads into size 0 hard gelatin capsules using a MG Futura capsule filling equipment. The drug release testing was performed using USP Apparatus 2 (Paddles @ 50 rpm) in 0.1N HCl for 2 hours and subsequently at pH 6.8. The release profiles generated from Pulsatile Release Capsules comprising TPR Beads with different
30 membrane coating levels are presented in Figure 2.

Example 2

Nizatidine (168 kg) was slowly added to an aqueous solution of hydroxypropylcellulose such as Klucel LF (18.6 kg) and mixed well. # 25-30 mesh sugar spheres (107.4 kg) were coated with the drug suspension in a Glatt fluid bed coater, equipped with a 32" bottom spray Wurster insert. The drug containing particles were dried, and a seal coat of Opadry Clear (2% w/w) was first applied and dried in the Glatt fluid bed unit as a precautionary measure to drive off excessive surface moisture. These drug containing IR Beads were provided with an outer membrane by spraying a solution of 1:1 blend of ethylcellulose and HPMCP plasticized with diethyl phthalate in 98/2 acetone/water in a fluid bed coater for a weight gain of approximately 39-40%. The coated particles are cured at 60°C for 4 hours to produce TPR Beads (batch size: 300 kg). Pulsatile Release Nizatidine Capsules, 150 mg, were manufactured by filling 75 mg IR Beads and 75 mg TPR beads into size 0 hard gelatin capsules. The drug release profile is shown in Figure 3.

Example 3

In order to assess the type of *in vitro* release profile needed to achieve a circadian rhythm effect under *in vivo* conditions, a modeling exercise was performed using the pharmacokinetic parameters for nizatidine. A diurnal variation in the pharmaco-kinetics of nizatidine has been reported by Jamali, A. Thomson, P. Kirdeikis, M. Tavernini, L. Zuk, R. Marriage, R. Simpson, and V. Mahachai (the reference entitled, "Diurnal variation in the pharmaco-kinetics of Nizatidine in healthy volunteers and in patients with peptic ulcer disease", *Journal of Clinical Pharmacology* 35:1071-1075, 1995 is incorporated in its entirety). A pharmaco-kinetic modeling was done separately to try to mimic both night time and day time results individually. Mean serum concentrations of nizatidine achieved in healthy volunteers were taken from the same literature. Theoretical *in vitro* dissolution profile (Figure 4) as well as *in vivo* serum levels achieved during nighttime and daytime dosing, were simulated using the pharmaco-kinetic models developed. The advantages of a pulsatile dosage form are evident in attached Figure 5 that compares simulated serum levels achieved with an immediate release dose of nizatidine versus the proposed pulsatile dose, being orally administered at (a) nighttime and (b) daytime. The proposed dosage form is seen to give two pulses about 3.5 – 4.0 hours apart, maintaining an acceptable serum concentration for about 6.0– 8.0 hours in the body, irrespective of whether night time or day time dosing is considered. Thus, the presence of the TPR portion should

ideally sustain enough drug in the body right around midnight when literature has reported a circadian rhythm to gastric acid secretion and increased severity of symptoms associated with GERD.

Clinical supplies, nizatidine pulsatile Capsules, 150 mg, comprising of 75 mg IR and 75 mg TPR Beads were manufactured following Example 1, by filling hard gelatin size# 0 capsules. Figure 6 shows the plasma concentration profile (a bimodal display) achieved in a healthy volunteer when dosed after dinner.

Example 4

The nizatidine pulsatile Capsules prepared in Example 3 were utilized in two randomized, double-blind, comparative, multiple dose efficacy studies. The clinical efficacy studies included a total of 428 subjects with GERD who were treated with the subject nizatidine Capsules and 215 treated with placebo. For the purpose of summarizing the nizatidine Capsules efficacy data, the two randomized, double-blind, comparative, multiple dose efficacy studies were conducted under identical protocols during the same time period, and identical case report forms were used for both studies. Clinical studies were designed to assess the safety and efficacy of nizatidine Capsules 150mg bid, nizatidine Capsules 300mg and placebo in adult subjects with clinical symptom and endoscopic evidence of erosive and ulcerative GERD. Subjects meeting the entry criteria were randomized to receive one of the three treatments and began taking study medication in the evening on Day 0. Study medication was taken for up to 12 weeks, with follow-up visits at weeks 3,6 and 12.

The results of the combined efficacy analyses indicated that clinically and statistically significant healing of erosive esophagitis with associated symptom relief was produced by the nizatidine Capsules administered either as individual doses (150mg bid) or as a single nightly dose of 300mg. For the nizatidine Capsule 150mg bid, statistically significant and clinically meaningful overall healing was also demonstrated. Subjects treated with nizatidine Capsules bid had a significantly greater mean change from baseline in their endoscopy grade and there was a notable trend toward efficacy in the proportions of subjects who had ≥ 2 points improvement in baseline endoscopy grade compared to those treated with placebo. Subjects treated with nizatidine Capsules 300mg qd also had a greater mean change from baseline in their endoscopy

grade. Based on subject rated nighttime symptom scores, statistically significant and clinically meaningful night time relief of heartburn, regurgitation and retrosternal pain was demonstrated during the first week of treatment for both nizatidine Capsules 150 mg bid and nizatidine Capsules 300 mg qd. Based on Investigator-rated night time symptom scores, treatment with nizatidine Capsules 150mg bid was significantly superior to placebo at Week 12 for heartburn and regurgitation, and there a trend toward efficacy for retrosternal pain. Treatment with nizatidine Capsules 300 mg qd was significantly superior to placebo at Week 12 for heartburn, regurgitation and retrosternal pain. Based on Investigator rated daytime symptom scores, treatment with nizatidine Capsules 150mg bid was significantly superior to placebo at Week 12 for daytime heartburn and retrosternal pain. Nizatidine Capsules 300mg qd was significantly superior to placebo at Week 12 for daytime retrosternal pain. Subjects treated with nizatidine Capsules 150mg bid used significantly less antacid tablets per day than did those treated with placebo ($P < 0.001$).

The study conclusion was as follows:

“Overall, in subjects with endoscopically proven GERD, nizatidine CR administered in doses of either 150 mg bid or 300 mg qd was effective in healing esophageal erosions and in relieving GERD symptoms.”

Example 5

Cimetidine was slowly added to an aqueous solution of polyvinylpyrrolidone and mixed well. # 25-30 mesh sugar spheres were coated with drug solution in a Glatt fluid bed granulator. The drug containing pellets were dried, and a seal coat of Opadry Clear (2% w/w) was first applied. The inner polymer coating was applied to the active particles by spraying an aqueous dispersion of ethylcellulose (aquacoat® ECD-30 with dibutyl sebacate as the plasticizer to produce intermediate release (IntR) Beads. An outer coating formulation was prepared by mixing two separate aqueous dispersions of Eudragit L30D plasticized with acetyl tri-n-butyl citrate and Aquacoat ECD-30 (an aqueous dispersion of ethylcellulose) plasticized with dibutyl sebacate. The combined coating formulation was sprayed onto the ethylcellulose coated IntR Beads. The coated particles are cured at 60°C until the polymers were coalesced to produce TSR Beads. The finished SR and TSR Beads were tested for *in vitro* dissolution properties using USP

Dissolution Apparatus 2 at a paddle speed of 50 rpm. The beads were dissolved using a three-stage dissolution medium, i.e., first 2 hours in 0.1N HCl, next 2 hours at pH 4.0 and then at pH 6.8 for additional 14 hours, the pH of the medium being changed by adding a pH modifier. The results obtained are presented in Table 1. The dissolution results show that there is a lag time of about four hours followed by sustained release occurring over a period of 12-14 hours for the TSR Beads.

Table 1: Dissolution Data for SR and TSR Beads of Example 4

Time, hours	SR Beads SR Coating (1.8% w/w)	TSR Beads SR Coating (1.8% w/w) / TSR Coating (15% w/w)
1.0	0.2	0
2.0	0.1	0
3.0	0.5	0.5
4.0	0.2	0.4
5.0	15	10
6.0	42	24
8.0	71	47
10.0	85	62
12.0	93	72
14.0	98	78
16.0	103	86

We claim: